Adverse events in patients taking cephalosporins versus placebo for any indication

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[Intervention Protocol]

Adverse events in patients taking cephalosporins versus placebo for any indication

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To quantify the incidence of any reported adverse event in patients taking cephalosporins compared with placebo for any indication.

BACKGROUND

Description of the condition

Use of cephalosporin antibiotics (known as cephalosporins) varies, with usage as low as 0.2% in Denmark and as high as 23.5% in Malta (ECDC 2014). Variations in cephalosporin use may be due to concerns about the development of antibiotic resistance. Indications include: respiratory tract infections (acute otitis media, bacterial sinusitis, severe pneumonia), bacterial meningitis, urinary tract infections, septicaemia, surgical prophylaxis, skin and soft tissue infections, and gonorrhoea (Australian Medicines Handbook 2015).

Description of the intervention

Cephalosporins are a subclass of the β-lactams. The list of International Nonproprietary Names, compiled by the World Health Organization (WHO), contains 80 cephalosporins (WHO 2016), all of which share a common β-lactam ring and have medium to broad spectrum activity against both Gram-positive and Gram-negative bacterial species (Rang 2015), including *Pseudomonas aeruginosa* (*P aeruginosa*), *Streptococcus pneumoniae* (*S pneumoniae*), *Staphylococcus aureus* (*S aureus*), *Haemophilus influenzae* (*H influenzae*), *Klebsiella pneumoniae* (*K pneumoniae*), and *Escherichia coli* (*E coli*) (Therapeutic Guidelines 2014). Cephalosporins are often referred to as first, second, or third generation, based on the order in which they were developed.
An adverse event is an adverse outcome that occurs while a patient is taking a drug, but the event is not (or not necessarily) attributable

to the drug taken (Edwards 2000).

It has been recommended that the recording of adverse events in clinical trials should distinguish suspected adverse effects from suspected adverse reactions (Aronson 2013), defined as follows.

1. Adverse effects are unwanted outcomes of which the patient is not aware; they are usually detected by laboratory tests (e.g. biochemical, haematological, immunological, radiological, pathological tests) or by clinical investigations (e.g. gastrointestinal endoscopy, cardiac catheterisation).
2. Adverse reactions are unwanted outcomes that the patient experiences and are detected by their clinical manifestations (symptoms and/or signs).
3. Serious adverse events are often reported separately. These are adverse events that occur at any dose, and result in death or life-threatening events; requirement for hospitalisation or prolongation of existing hospitalisation; persistent or significant disability; or congenital anomalies; or are events that are considered medically important (ICH 2003).

Recent guidance suggests that clinical trial authors should report all adverse events that occur in more than 5% of any group (Zarin 2016). The events can be classified by the 27 System Organ Classes (e.g. blood and lymphatic system disorders) defined by the Medical Dictionary for Regulatory Activities (MedDRA) or the 335 High Level Group Terms of this classification (MedDRA 2016).

How the intervention might work

Antibiotics can cause unwanted events in different ways.

1. Hypersensitivity reactions, in which the host generates an immune response to the drug, perhaps manifesting as a rash (Ibia 2000), and which can occur even at doses that are below the usual therapeutic range.
2. Adverse reactions that occur at doses in the usual therapeutic range (called collateral reactions). Some of these can occur through direct adverse effects (e.g. nausea and vomiting due to altered gastric emptying; Kuo 1998); and others through destruction of commensals (disturbing the equilibrium of the microbiome, which might cause diarrhoea from an overgrowth of Clostridium difficile (*C difficile*); or thrush from an overgrowth of Candida).
3. Adverse reactions that occur at high doses (toxic reactions).
4. Induction of antibiotic resistance in micro-organisms in the microbiome, which may affect individuals in the general population. Since resistance can be transmitted between organisms, the risk of harm from resistant micro-organisms extends beyond the individual. It is not possible to determine the extent of this harm from individually randomised trials, and this is therefore beyond the scope of the current review.

Why it is important to do this review

Adverse events in those taking antibiotics are usually measured by observational mechanisms: anecdotal reporting; voluntary organised reporting; intensive event monitoring; and observational research studies (Edwards 2000). These approaches are susceptible to reporting biases (Edwards 2000); and misclassification of the cause of events which could be due to the antibiotic or the underlying disease for which it was prescribed. Randomised controlled trials (RCTs) of antibiotics, the gold standard for determining efficacy of interventions, are often underpowered to detect differences in adverse events (Chen 2014). Several systematic reviews of RCTs in the Cochrane Library have reported on adverse events in those taking cephalosporins (Kilburn 2010; Paul 2010), but noted that there were insufficient data on adverse events to make clear conclusions (Kilburn 2010). One way of overcoming this problem is to carry out a 'multi-indication' review i.e. a review of the effects of an intervention in all participants using the intervention for any reason (indication). This type of review is particularly useful for detecting rare events like adverse events, where the mechanism of action is unrelated to the indication (Chen 2014). This review is the third in a series of multi-indication reviews investigating adverse events in those taking antibiotics (Gillies 2015; Plejdrup Hansen 2015).

OBJECTIVES

To quantify the incidence of any reported adverse event in patients taking cephalosporins compared with placebo for any indication.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will exclude pharmacodynamic studies of events that are not considered to be adverse events (e.g. studies that test gastrointestinal motility after ingestion of cephalosporins); pharmacokinetic studies of events that are not considered to be adverse events (e.g. testing interactions with other drugs); and studies with less than 20 participants randomised to each arm.

Types of participants

We will include individuals of all ages taking cephalosporins for any indication.

Types of interventions

We will include trials comparing cephalosporins delivered by any route (per oral, intravenous, intramuscular, or per rectal) with placebo. Use of concomitant medications is permitted.

Types of outcome measures

Primary outcomes

1. A composite outcome of all adverse events of any kind (that occur in 5% or more of any group; Zarin 2016).
2. Serious adverse events.
3. Subsequent carriage of resistant bacteria (measured at any time point post-treatment).

Secondary outcomes

1. Adverse events (that occur in 5% or more of any group; Zarin 2016) organised by System Organ Classes listed in the MedDRA, and where there is enough information, High Level Terms of this classification (MedDRA 2016).

Reporting one or more of the outcomes listed here in the trial is not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will search the following databases from inception to present.

1. CENTRAL (Cochrane Central Register of Controlled Trials).
2. PubMed (MEDLINE).
3. Embase.

We will use the search strategy described in Appendix 1 to search CENTRAL (Cochrane Central Register of Controlled Trials), which contains the Cochrane Acute Respiratory Infections (ARIs) Group's Specialised Register and PubMed (MEDLINE). We will use the Cochrane Highly Sensitive Search Strategy for randomised trials: sensitivity and precision-maximising version (2008 revision) (Lefebvre 2011). We will adapt the search strategy to search Embase. We will also conduct a search of the WHO International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch), which contains ClinicalTrials.gov (www.ClinicalTrials.gov). We will not impose language, publication date, or publication status restrictions.

To develop the search strategy, one of the review authors (JA) provided a list of common cephalosporins from the WHO list of International Nonproprietary Names (WHO 2016; see Appendix 2). After an initial review of the search results using this list in the search strategy, we decided to supplement it with additional terms. We did this using a four-step process.

1. We identified all cephalosporins listed in the Mesh database as well as any relevant entry terms from their MeSH entries and combined this list with the original list provided by the review author; this gave a list of 186 terms.
2. We removed trade names from the list; this left 127 terms.
3. Where a term contained an 'f', for example, cefazolin, we added a new term using 'ph' instead, for example, cephazolin. This created a list of 206 terms.
4. One of the review authors (JA) undertook a final check of the terms to remove any remaining trade names. This left 158 terms which were incorporated into the search strategy.

Searching other resources

We will conduct a forward and backward citation analysis of all included studies to look for additional references. We will contact the authors of trials of cephalosporins versus placebo and ask for adverse events data if they are not published.

Data collection and analysis

Selection of studies

Pairs of review authors (AMcC, AS, CM) will independently screen titles and abstracts resulting from the searches. We will retrieve all potentially eligible full-text articles for full-text screening. Pairs of review authors (AMcC, AS, CM) will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (CDM or EB). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009), and 'Characteristics of excluded studies' table.

Data extraction and management

Pairs of review authors (AMcC, AS, CM) will independently extract the following data using a standardised data extraction form (piloted on at least one study in the review), which will include the following information.

1. Methods: study design, year of publication, clinical trial registration, study setting, study population, and information to assess risk of bias (see below).
2. Participants: N, mean age or age range, gender.
3. Interventions: intervention (indication, route of administration, dose, and duration), comparison, and concomitant medications.

4. Outcomes: any adverse events reported, times of measurements, and the methods used to elicit adverse events data.

5. Notes: funding for trial, and notable conflicts of interest of trial authors.

We will note in the 'Characteristics of included studies' table if outcome data are not reported in a usable way. We will resolve disagreements by consensus or by involving a third review author (CDM or EB).

Assessment of risk of bias in included studies

Pairs of review authors (AMcC, AS, CM) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another review author (CDM or EB). We will assess the risk of bias according to:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting; and
7. other bias.

We will grade each potential source of bias as 'high', 'low' or 'unclear' and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed using a 'Risk of bias' summary figure. We will consider blinding separately for different key outcomes, where necessary. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

Where possible, we will enter the outcome data for each study into the data tables in Review Manager 5 to calculate the treatment effects (RevMan 2014). We plan to express all outcomes as Peto odds ratios (ORs), with accompanying 95% confidence intervals (CIs), as we assume that the included trials will report few adverse events. However, we will only use this approach on condition of meeting the relevant criteria for using Peto's method as stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

1. when interventions effects are small;
2. when events are not particularly common; and
3. the studies have similar numbers in the experimental and control group.

We will express ORs as absolute risk differences (RDs), based on assumed/average rates of adverse events in the control groups, and convert to the number needed to treat to harm (NNTH) to interpret the results from the meta-analysis. We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense.

Unit of analysis issues

We will use the patient as the unit of analysis, where reported. If antibiotic resistance is reported by proportion of isolated bacteria (rather than by patient), then we will use this as the unit of analysis.

Dealing with missing data

We will contact trial authors to obtain additional information if reporting of data is incomplete or if the data are missing. If no information about missing data is available, and the data are thought to introduce bias, we will explore the impact of including such studies in the overall results using a sensitivity analysis.

Assessment of heterogeneity

We will use: (1) visual inspection of forest plots; (2) statistical test of heterogeneity (Chi^2 test); and, (3) measure of inconsistency (I^2 statistic) to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity (> 50%), we will report it and explore possible causes by prespecified subgroup analysis (Higgins 2011).

Assessment of reporting biases

We will minimise reporting bias by conducting a comprehensive search for relevant study protocols and unpublished trials. Outcome reporting bias may be particularly important for adverse events, and we will clarify whether all outcomes listed in the study protocols are published and whether the outcomes were predefined (Higgins 2011). If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study and publication biases.

Data synthesis

We will pool data from studies we judge to be clinically homogeneous using Review Manager 5 software (RevMan 2014). If more than one study provides usable data in any single comparison, we

will perform a meta-analysis. We will summarise every reported adverse event with a meta-analysis of the OR using fixed-effects models presented with 95% CIs. Where it is not possible to combine data statistically, we will report outcomes narratively.

GRADE and 'Summary of findings' table

We will create a 'Summary of findings' table which will include the following outcomes: a composite outcome of all adverse events of any kind (that occur in 5% or more of any group; Zarin 2016); serious adverse events; subsequent carriage of resistant bacteria (measured at any time point post-treatment); and, adverse events (that occur in 5% or more of any group; Zarin 2016) organised by System Organ Classes listed in the MedDRA, and where there is enough information, High Level Terms of this classification (MedDRA 2016). We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro software (GRADEpro GDT 2014). We will justify all decisions to down- or upgrade the quality of studies using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Age groups (children or adults).
2. First, second, or third generation of cephalosporin.
3. Route of administration (per oral, intravenous, intramuscular, per rectal).
4. Antibiotic dosage (dose and frequency of administration).
5. Duration of therapy.

We will use the Chi² test to test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We will perform a sensitivity analysis by excluding those studies found to have a high risk of bias. If a study has more than 20% of randomised participants with missing data for the outcome (lost to follow-up/reporting of adverse events), we will exclude it from the primary analysis, but include it in a sensitivity analysis.

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REFERENCES

Additional references

Aronson 2013
Aronson 2013. Distinguishing hazards and harms, adverse drug effects and adverse drug reactions: implications for drug development, clinical trials, pharmacovigilance, biomarkers, and monitoring. *Drug Safety* 2013;**36**(3): 147–53.

Atkins 2004
Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; **328**(7454):1490.

Australian Medicines Handbook 2015
Australian Medicines Handbook. *Australian Medicines Handbook*. Adelaide: Australian Medicines Handbook Pty Ltd, 2015.

Chen 2014
Chen YF, Hemming K, Chilton PJ, Gupta KK, Altman DG, Lilford RJ. Scientific hypotheses can be tested by comparing the effects of one treatment over many diseases in a systematic review. *Journal of Clinical Epidemiology* 2014;**67**(12):1309–19.

ECDC 2014
European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe 2012. Stockholm: ECDC 2014.

Edwards 2000
Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000;**356** (9237):1255–9.

Gillies 2015
Gillies M, Ranakusuma A, Hoffmann T, Thorning S, McGuire T, Glasziou P, et al. Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication. *Canadian Medical Association Journal* 2015;**187**(1):E21–31.

GRADEpro GDT 2014 [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Higgins 2011
Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Ibia 2000
Ibia EO, Schwartz RH, Wiedermann BL. Antibiotic rashes in children: a survey in a private practice setting. *Archives of Dermatology* 2000;**136**(7):849–54.

ICH 2003
International Conference on Harmonisation. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Post-approval safety data management: definitions and standards for expedited reporting. www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf 2003 (accessed 09 November 2016).

Kilburn 2010
Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. *Cochrane Database of Systematic Reviews* 2010, Issue 6. [DOI: 10.1002/14651858.CD004299.pub2]

Kuo 1998
Kuo WH, Wadwa KS, Ferris CD. Cephalosporin antibiotics accelerate gastric emptying in mice. *Digestive Diseases and Sciences* 1998;**43**(8):1690–4.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

MedDRA 2016
Medical Dictionary for Regulatory Activities. www.meddra.org 2016 (accessed 09 November 2016).

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. *BMJ* 2009;**339**: 2535.

Paul 2010
Paul M, Yahav D, Bivas A, Fraser A, Leibovici L. Anti-pseudomonal beta-lactams for the initial, empirical, treatment of febrile neutropenia: comparison of beta-lactams. *Cochrane Database of Systematic Reviews* 2010, Issue 11. [DOI: 10.1002/14651858.CD005197.pub3]

Plejdrup Hansen 2015
Plejdrup Hansen MP, Thorning S, Aronson JK, Beller EM, Glasziou P, Hoffmann TC, et al. Adverse events in patients taking macrolide antibiotics versus placebo for any indication. *Cochrane Database of Systematic Reviews* 2015, Issue 8. [DOI: 10.1002/14651858.CD011825]

Rang 2015
Rang HP, Ritter JM, Flower RJ, Henderson G. *Rang & Dale's Pharmacology*. 8th Edition. London: Elsevier Churchill Livingstone, 2015.

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Therapeutic Guidelines 2014
Antibiotic Expert Groups. Antibiotic. *Therapeutic Guidelines - Version 15*. Melbourne: Therapeutic Guidelines Limited, 2014.

WHO 2016
World Health Organization. International Nonproprietary Names. www.who.int/medicines/services/inn/en/ (accessed 16 August 2016).

Zarin 2016
Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov - the final rule. New England Journal of Medicine 2016 Sep 16 [Epub ahead of print]. [DOI: 10.1056/NEJMsr1611785]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Pubmed (MEDLINE) search strategy

("Cephalosporins"[Mesh] OR Cephalosporins[tiab] OR Cephalosporin[tiab] OR Cephalosporanic[tiab] cefacetrile[tiab] OR cefadroxil[tiab] OR cefaclor[tiab] OR cefadroxil[tiab] OR cefalexin[tiab] OR cefaloglycin[tiab] OR cefalonium[tiab] OR cefaloram[tiab] OR cefaloridine[tiab] OR cefalotin[tiab] OR cefamandole[tiab] OR cefaparole[tiab] OR cefapirin[tiab] OR cefatriaxone[tiab] OR cefatrizine[tiab] OR cefazaflur[tiab] OR cefazedone[tiab] OR cefazolin[tiab] OR cefbuperazone[tiab] OR cefcanel[tiab] OR cefcapene[tiab] OR cefclidin[tiab] OR cefdaloxime[tiab] OR cefdinir[tiab] OR cefditoren[tiab] OR cefedrolor[tiab] OR cefempidone[tiab] OR cefepime[tiab] OR cefetamet[tiab] OR cefetecol[tiab] OR cefetrizole[tiab] OR cefiderocol[tiab] OR cefilavancin[tiab] OR cefivitril[tiab] OR cefixime[tiab] OR cefluprenam[tiab] OR cefmatilen[tiab] OR cefmenoxime[tiab] OR cefmepidium[tiab] OR cefmetazole[tiab] OR cefminox[tiab] OR cefodizime[tiab] OR cefonicid[tiab] OR cefoperazone[tiab] OR ceforanide[tiab] OR cefoselis[tiab] OR cefotaxime[tiab] OR cefotetan[tiab] OR cefotiam[tiab] OR cefovecin[tiab] OR cefoxazole[tiab] OR cefoxitin[tiab] OR cefozopran[tiab] OR cefpimizole[tiab] OR cefpiramide[tiab] OR cefpirome[tiab] OR cefpodoxime[tiab] OR cefprozil[tiab] OR cefquinome[tiab] OR cefradine[tiab] OR cefrotil[tiab] OR cefroxadine[tiab] OR cefsulodin[tiab] OR cefsumide[tiab] OR ceftaroline[tiab] OR ceftazidime[tiab] OR cefteram[tiab] OR ceftezole[tiab] OR ceftibuten[tiab] OR ceftiofur[tiab] OR ceftiolene[tiab] OR ceftioxide[tiab] OR ceftizoxime[tiab] OR ceftobiprole[tiab] OR ceftolozane[tiab] OR ceftriaxone[tiab] OR cefuracetime[tiab] OR cefuroxime[tiab] OR cefuzonam[tiab] OR cephacetrile[tiab] OR cephadroxil[tiab] OR cephaclor[tiab] OR cephadroxil[tiab] OR cephalexin[tiab] OR cephaloglycin[tiab] OR cephalonium[tiab] OR cephaloram[tiab] OR cephaloridine[tiab] OR cephalotin[tiab] OR cephamandole[tiab] OR cephaparole[tiab] OR cephapirin[tiab] OR cephatriaxone[tiab] OR cephatrizine[tiab] OR cephazaflur[tiab] OR cephazedone[tiab] OR cephazolin[tiab] OR cephbuperazone[tiab] OR cephcanel[tiab] OR cephcapene[tiab] OR cephclidin[tiab] OR cephdaloxime[tiab] OR cephdinir[tiab] OR cephditoren[tiab] OR cephedrolor[tiab] OR cephempidone[tiab] OR cephepime[tiab] OR cephetamet[tiab] OR cephetecol[tiab] OR cephetrizole[tiab] OR cephiderocol[tiab] OR cephilavancin[tiab] OR cephivitril[tiab] OR cephixime[tiab] OR cephluprenam[tiab] OR cephmatilen[tiab] OR cephmenoxime[tiab] OR cephmepidium[tiab] OR cephmetazole[tiab] OR cephminox[tiab] OR cephodizime[tiab] OR cephonicid[tiab] OR cephoperazone[tiab] OR cephoranide[tiab] OR cephoselis[tiab] OR cephotaxime[tiab] OR cephotetan[tiab] OR cephotiam[tiab] OR cephovecin[tiab] OR cephoxazole[tiab] OR cephoxitin[tiab] OR cephozopran[tiab] OR cephpimizole[tiab] OR cephpiramide[tiab] OR cephpirome[tiab] OR cephpodoxime[tiab] OR cephprozil[tiab] OR cephquinome[tiab] OR cephradine[tiab] OR cephrotil[tiab] OR cephroxadine[tiab] OR cephsulodin[tiab] OR cephsumide[tiab] OR cephtaroline[tiab] OR cephtazidime[tiab] OR cephteram[tiab] OR cephtezole[tiab] OR cephtibuten[tiab] OR cephtiofur[tiab] OR cephtiolene[tiab] OR cephtioxide[tiab] OR cephtizoxime[tiab] OR cephtobiprole[tiab] OR cephtolozane[tiab] OR cephtriaxone[tiab] OR cephuracetime[tiab] OR cephuroxime[tiab] OR cephuzonam[tiab])
AND
("Placebos"[Mesh] OR Placebos[tiab] OR Placebo[tiab] OR "Sham treatment"[tiab])
AND
((randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR randomized[Title/Abstract] OR randomised[Title/Abstract] OR placebo[Title/Abstract] OR "drug therapy"[MeSH Terms] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract]) NOT (Animals[Mesh] not (Animals[Mesh] and Humans[Mesh]/)))

Appendix 2. List of all cephalosporin antibiotics (International Nonproprietary Names)

cefacetrile
cefaclor
cefadroxil
cefalexin
cefaloglycin
cefalonium
cefaloram
cefaloridine
cefalotin
cefamandole
cefaparole
cefapirin

cefatrizine
cefazaflur
cefazedone
cefazolin
cefbuperazone
cefcanel
cefcanel daloxate
cefcapene
cefclidin
cefdaloxime
cefdinir
cefditoren
cefedrolor
cefempidone
cefepime
cefetamet
cefetecol
cefetrizole
cefiderocol
cefilavancin
cefivitril
cefixime
cefluprenam
cefmatilen
cefmenoxime
cefmepidium chloride
cefmetazole
cefminox
cefodizime
cefonicid
cefoperazone
ceforanide
cefoselis
cefotaxime
cefotetan
cefotiam
cefovecin
cefoxazole
cefoxitin
cefozopran
cefpimizole
cefpiramide
cefpirome
cefpodoxime
cefprozil
cefquinome
cefradine
cefrotil
cefroxadine
cefsulodin
cefsumide
ceftaroline fosamil
ceftazidime

cefteram
ceftezole
ceftibuten
ceftiofur
ceftiolene
ceftioxide
ceftizoxime
ceftizoxime alapivoxil
ceftobiprole
ceftobiprole medocaril
ceftolozane
ceftriaxone
cefuracetime
cefuroxime
cefuzonam

CONTRIBUTIONS OF AUTHORS

1. Chris Del Mar (CDM): conceived the original idea for this review.

2. Amanda McCullough (AMcC): was responsible for drafting the protocol.

3. All authors: contributed to the drafting of the protocol and agreed the final version for publication.

DECLARATIONS OF INTEREST

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6. Elaine Beller: co-investigator on National Health and Medical Research Council (NHMRC) funded Centre for Research Excellence grant on antibiotic resistance.

7. Jeffrey K Aronson: JKA is a President Emeritus of the British Pharmacological Society, a Member of the Advisory Board of the British National Formulary, a Member of a Technology Appraisal Committee of the UK's National Institute for Health and Care Excellence (NICE), Chair of the Expert Advisory Group on Nomenclature, British Pharmacopoeia Commission, and Editor of textbooks on adverse drug reactions, including 'Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions.' He has published papers in peer-reviewed journals on different aspects of adverse drug reactions.

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